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Overlooked Elements in the History of evo-devo: Studies of Epigenetics in the 80s

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Since around 2000, much historical and philosophical consideration on evolutionary developmental biology (for short, "evo-devo") has been accumulated. This article is a part of such consideration; we focus on the prehistory of evo-devo and aim to demonstrate the importance and uniqueness of one of the trends that rethought the relationship between evolution and development in the 1980s, that is, the "anti-gene-centrism". We show that the anti-gene-centrism in the 80s challenged the gene-centered framework commonly held in the modern synthesis by integrating the methods and results of comparative morphology on the one hand, and those of experimental embryology on the other hand. We argue that such characteristics plausibly had important influences on the birth of evo-devo though the contribution to evo-devo have rarely been mentioned in previous historical and philosophical researches.

Here is the outline of this paper. First, we briefly summarize the previous studies by historians on evo-devo. Second, specific examples of the anti-gene-centric researches in the 80s by Alberch, Hall, and Müller are examined. We argue that their claims and methodology were novel, and point out that they have rarely been mentioned in the context of the development of evo-devo. Finally, we suggest that the anti-gene-centrism had important influences on evo-devo today.

History of evo-devo: A brief summary of the previous works

In the past studies on the historical background of evo-devo, we can distinguish several trends. First, some have focused on which disciplines have contributed to evo-devo today, and often emphasized the role of developmental genetics (e.g., Gilbert

2003; Carroll 2005) and comparative studies (Love and Raff 2003). For instance, Love and Raff (2003) argue that we should look not only at developmental genetics but also at comparative embryology, morphology and paleontology because the techniques and tools used in evo-devo today had been created in the tradition of developmental genetics, and the research problem including the relationship between evolution and development in evo-devo had long been studied in the latter disciplines. The second trend is the consideration of individual contributions by pioneers of evo-devo such as Haeckel, Goldschmidt, Waddington and so on (e.g., Laubichler and Maienschein 2007).

Although the previous historical studies have focused on a long-term history from 1880s to 1990s or some pioneers' works, they have not paid much attention to the 80s. Some researches mention the challenges to the modern synthesis offered by diverse disciplines (e.g., paleontology, morphology, comparative embryology, and developmental biology) around the 80s and emphasize the importance of developmental genetics, which is said to have brought together the diverse movements and laid the foundation for evo-devo (Love and Raff 2003; Laubichler 2009, 2010). However, more detailed analyses of the 80s are needed because it was the era just prior to the birth of evo-devo[1] and therefore it is important in the prehistory of evo-devo. Thus by focusing on the 80s, the present study intends to make up the lack of the previous studies.

Empirical studies on epigenetics: Methodological integration and non-gene-centered framework

This section summarizes some empirical works of the anti-gene-centrism such as researches by Alberch, Hall, and Müller, emphasizing the role of non-genetic developmental processes and integrating the methodology of experimental embryology and comparative studies. Before examining them, however, we clarify the word "anti-gene-centrism" and the concept "epigenetics," which was emphasized by the anti-gene-centrists.

What are epigenetics and the anti-gene-centrism?

The concept of "epigenetics" was coined by Waddington (1942) and it originally

represented the entire mechanism of development through which phenotypes are formed from genotypes including elements that did not fit in the gene-centered framework squarely, such as developmental constraint, phenotypic plasticity, and tissue interaction. In the 80s, the notion "epigenetics" was used in several different manners. In some cases, it was used in the original sense, where the entire mechanism including both genes and developmental processes is referred to. In other cases, it was contrasted with "genetics," which implied that epigenetics referred to aspects that were not included in genetics. The present article uses the term in the original manner.

There was a trend in the 80s that emphasized the importance of epigenetics for evolution and would modify and improve the evolutionary theory by demonstrating the evolutionary significance of development. The trend included three researchers, Pere Alberch, Brian K. Hall and Gerd B. Müller. We refer to the trend as the "anti-gene-centrism." Two points should be noticed on the expression. First, Alberch, Hall, and Müller did not mention themselves as the anti-gene-centrists and also their studies are not and have not been considered as being included in one individual trend. However, this paper regards their studies in the 80s as belonging to the individual trend "anti-gene-centrism" because they shared similar characteristics and they have referred to each other. Second, the anti-gene-centrists intended not to entirely reject the gene-centered framework held by the modern synthesis but to supplement and improve it. This point is explained in detail in the section 3.3.

The anti-gene-centric studies by Alberch, Hall, and Müller (1): Methodological integration

Let us move on to some concrete examples of the anti-gene-centric studies in the 80s. One of their characteristics is an integration of the methodologies and results of comparative morphology on the one hand, and those of experimental embryology on the other hand. For instance, first, based on the methodology of comparative morphology (i.e., comparing morphologies between different lineages to reveal evolutionary history of the morphologies), Alberch and Gale (1985) compared patterns of digital loss of frog lineage and salamander lineage, and showed that there were different patterns of digital loss between them. Next, following the methodology of experimental embryology

(i.e., intervening developmental processes of the organisms to reveal mechanisms of the processes), they experimentally reduced the number of cells in limb buds using colchicine as the mitotic inhibitor in each lineage. They demonstrated that the same patterns as those observed in natural populations were produced by the experiment. Thus by integrating the methodologies from different disciplines, they concluded that the morphologies of digits of frogs and salamanders were determined not by genetic or selective factors but by developmental constraints.

Hall (1984) also drove the integration of the different methods by synthesizing results of a number of articles of comparative morphology and experimental embryology. Referring to numerous comparative studies of the limb-formation mechanism of vertebrates, Hall argued that various regression of limb in vertebrates could be explained in terms of decrease in the number of cells in limb bud. He also analyzed results from experimental embryology, among which the experiment by Kollar and Fisher (1980) is a good example. In this experiment, Kollar and Fisher demonstrated that chick epithelium generated tooth when cultured with mouse mesenchyme (see also Hall 1984, pp. 115-116), suggesting that the lack of teeth in birds is not due to the loss of the genetic ability to make them but that of the tissue interaction necessary to make them. By synthesizing these analyses, Hall concluded that at least some kinds of atavisms were not based on changes in genomes, rather that they were induced by changes in developmental mechanisms.

Just like Hall (1984), Müller (1990) drove the integration of much information from comparative morphology and experimental embryology. For example, Müller cited some comparative studies demonstrating that changes in quantitative traits (e.g., body size) correlated with changes in qualitative traits (e.g., shapes of limbs) by comparing them in various lineages of lizard. He interpreted the results as the evidence that evolutionary novelties were able to emerge as by-products of quantitative changes. He also argued that some epigenetic mechanism helps morphological novelties be coordinated with other structures of the organisms. In order to support this hypothesis, he referred to some studies of experimental embryology, one of which was an experiment where the eye primordium of a large species of salamander was transplanted to the head of a small species of salamander. As the result of this transplantation, related

structures (e.g., the ocular muscles and the optic nerves) of the host changed their morphologies coordinately. Thus as Alberch and Hall did, by driving the integration of the methodologies of comparative morphology and experimental embryology, Müller constructed a theory of developmental mechanisms of the appearance of evolutionary novelty.

Thus, they employed the novel methodology that was the combination of the methods of and results from comparative morphology and experimental embryology. Moreover, they were aware of the novelty and importance of it. For example, Alberch and Gale (1985) said that "[i]n this study, we *integrate information from phylogeny, comparative ontogeny, and experimental embryology*" (Alberch and Gale 1985, p. 8; emphasis ours). Also Müller and Streicher (1989) argued that "[w]e analyze the structural, developmental and adaptive aspects of its origin *in a combined descriptive, experimental, and comparative approach*" (Müller and Streicher 1989, p. 327; emphasis ours). So the conscious integration of the different methodologies is one of the important characteristics of the anti-gene-centric studies.

The anti-gene-centric studies by Alberch, Hall, and Müller (2): Non-gene-centered framework

Let us move on to the other characteristic of the anti-gene-centric studies in the 80s; the challenge to the gene-centered framework. Alberch, Hall and Müller argued that genomes did not contain all the information of morphology and that epigenetic factors played important roles for generation of morphologies. First, Alberch emphasized the importance of developmental constraints (Alberch 1980; Alberch 1982; Alberch and Gale 1985). Both in natural populations and experimental conditions, some kinds of morphological changes were more likely to be found than others. According to him, such directionalities of possible morphologies were explained in terms of developmental mechanisms. Second, Hall also emphasized the importance of developmental mechanisms, but in his case the emphasis was on tissue interactions (Hall 1983; Hall 1984). As various experiments and observations showed, organismal structures could drastically change their morphologies by changes in tissue interactions (Hall 1983, pp. 374-375). Finally, Müller mainly investigated novel traits that emerged as by-products

or side effects of changes in other traits (Müller 1989; Müller and Streicher 1989; Müller 1990). He argued that in the cases of these kinds of characters, genetics was able to explain only the first quantitative changes, and that in order to understand the secondary qualitative changes, we should look at developmental processes (Müller 1990, p. 121). Thus according to the anti-gene-centrism, the role played by genome in determining organisms' morphologies is much less important and that of developmental conditions much more essential than previously thought.

Moreover, they (especially Alberch and Müller) also criticized the gene-centered framework as inadequate for evolutionary studies. Both Alberch and Müller pointed out that it was inappropriate to consider evolution just as changes in the gene frequencies (Alberch 1980, p. 664; Müller 1990, p. 99). Furthermore, they argued "there is generally little correlation between rates of structural gene evolution and rates of morphological diversification" (Alberch 1980, p. 664), or "alterations of the genome are to some extent peripheral to the problem of morphological change" (Müller 1990, p. 99). Hall also said "Development is controlled epigenetically. Evolution acts by altering development" (Hall 1983, p. 374). Thus, the anti-gene-centrism criticized the trend in the modern synthesis overemphasizing genes from both developmental and evolutionary viewpoints.

It is noteworthy, however, that they did *not completely* deny the importance of genes. Alberch clearly stated that his own analyses of developmental constraints were able to be compatible with the approaches of genetics (Alberch 1982, p. 328). Hall also emphasized that his own analyses of epigenetic mechanisms did not obstruct Darwinian evolutionary theory (Hall 1984, p. 90). Müller clearly said "the primary causes of evolution are Darwinian" (Müller 1990, p. 121) and admitted that original quantitative changes (necessary for novel qualitative changes to emerge as "side-effects") emerged through genetic processes.

Therefore, their attempts were not to reject or to replace the gene-centered framework in the modern synthesis by epigenetics, but to supplement and improve it. The following words by Hall clearly expressed this point: "The challenge for the evolutionary biologists is to *integrate epigenetic control into evolutionary theory* so that its role in generating, while at the same time limiting, diversity may be clarified" (Hall 1983, p. 374; emphasis ours).

Influence on evo-devo today

In previous sections, we have seen what characteristics the anti-gene-centrism in the 80s had. In this section, let us analyze how they influenced the area that we call evo-devo now. In 1992, the book *Evolutionary Developmental Biology* was published, after which the area "evolutionary developmental biology" was named and which is regarded as "the first textbook of evo-devo" (Laubichler and Maienschein 2007; Robert 2008). In this book, Hall mentioned the anti-gene-centric studies in the 80s and emphasized its importance:

> Given the two premises that vertebrate development is built upon epigenetic cascades, and that variation in the heritable and repeatable portions of epigenetic processes provides a mechanism for modification of form and structure during evolution (Gould, 1977; Hall, 1982a, 1984b, 1990b; Alberch, 1985, and see Chapters 8 and 9), […] it will be important to identify further epigenetic cascades and to understand their cellular, molecular and genetic bases, in the continued search for mechanisms underlying evolutionary developmental biology. (Hall 1992, p. 119)

Many of the studies cited in this quote are the anti-gene-centric studies discussed here.

The following quote is more important because it indicates that epigenetics was considered as at least one of the *central* principles of evolutionary developmental biology: "[T]he integration of epigenetics, genomic and environmental control provides such a principle for evolutionary developmental biology" (Hall 1992, p. 215).

Furthermore, Hall referred to the studies done by Alberch in the context of morphogenetic mechanisms; "Alberch has documented the importance of epigenetic control as a basis for morphological change (Alberch et al. 1979; Alberch, 1980; Alberch and Alberch, 1981)" (Hall 1992, p. 124). He also mentioned the studies done by Müller in the context of the epigenetic mechanisms generating evolutionary novelty; "Müller (1990) has outlined an approach to such integrated analyses. Because functionally interdependent structures are tightly epigenetically coupled in development innovations could arise as secondary by-products of epigenetic change during development, or as side-effects of phylogenetic change in size or developmental timing" (Hall 1992, p. 146).

So the fact that the epoch-making book emphasized the importance of the anti-gene-centrism in the 80s suggests that they had much influence on the birth of evo-devo. Moreover, as mentioned before, the anti-gene-centrism in the 80s intended to supplement and improve the modern synthesis and today's evo-devo includes similar attempts (Hall 2000; Gilbert 2003; Robert 2004; Laubichler 2009). Therefore it is plausible that the anti-gene-centrism was one of the origins of several aspects of evo-devo that go beyond the modern synthesis.

One might argue that the above arguments are trivial: It is truism that the studies by the author of "the first textbook of evo-devo" was regarded as important in evo-devo. As stated earlier, however, what we would like to argue is that the previous researches on the development of evo-devo have not paid much attention to the importance of the anti-gene-centrism in the 80s. The previous studies have emphasized only developmental genetics and comparative studies because they provided the research topics and the techniques in evo-devo today. If we are right, however, the anti-gene-centrism is one of the origins of the important aspects of evo-devo today. Thus in order to reconstruct the whole development of evo-devo, historical researches on the anti-gene-centrism in the 80s are needed.

Conclusion

The anti-gene-centrism was a unique trend to rethink the relationship between evolution and development in the 80s. It challenged the gene-centered framework and argued that the modern synthesis should be supplemented and improved by integrating the methodologies of and results from comparative morphology and experimental embryology, and moreover, they have plausibly much influenced evo-devo today.

Notes

1. Although there are various views on the time when evo-devo came into existence (Müller 2007; Laubichler 2009; Arthur 2011), this paper regards it as the early 1990s.

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